The Use of Active Surveillance Cultures to Reduce Methicillin-Resistant Staphyloccocus aureus-Related Morbidity, Mortality, and Costs: A Systematic Review

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ABSTRACT

Introduction Hospital-acquired infections are a frequent and serious public health problem. More than 60% of intensive care unit patients with Staphylococcus aureus have a methicillin-resistant form. Active surveillance cultures (ASCs), which are universal or targeted screening cultures of patients admitted to a hospital unit, have been proposed to control the increasing numbers of infections caused by multi-drug resistant organisms. Infection control groups and policy makers have an interest in ASCs, but this method is controversial because it is unclear if it reduces morbidity and mortality and if it is cost-effective.

Methods A systematic review of the literature pertaining to the use of ASCs and control of methicillin-resistant Staphylococcus aureus (MRSA) was conducted. The literature search included PubMed MEDLINE (1966 - present), Web of Science (1955 - present), CINAHL (1982 - present), the Cochrane Library, and a hand search of six infection control journals from 2000-2007 and the reference lists of the included articles. Two independent reviewers selected the primary research studies to be included. Included articles were summarized and assigned quality ratings.

Results Sixteen observational studies and four economic analyses were included in this systematic review. Only two of the sixteen (12.5%) observational studies had a control group. None of the studies were of high quality. No randomized controlled trials were identified.

Discussion This review identified many gaps within the literature, including a need for a clear definition of ASCs, a clear implementation protocol that includes a defined screening group and laboratory methods, and rigorous economic evaluations. Existing evidence favors the use of ASCs, but the overall quality is so low that definitive recommendations cannot be made.

INTRODUCTION

Purpose of the Master's Paper

Hospital-acquired infections are a frequent and serious public health problem, and their management and control are essential to minimize hospital-related morbidity and mortality.[1] Some of the most challenging causes of hospital-acquired infections involve multi-drug resistant organisms, including methicillin-resistant Staphylococcus aureus (MRSA).[1,2] There are numerous infection control methods that hospitals and other health care facilities employ; however, increasing numbers of infections are caused by multi-drug resistant organisms. One possible infection control measure is active surveillance culturing of patients admitted to hospitals or other health care facilities. However, there is not a clear definition of what constitutes an "active surveillance culture" and how it should be used. There is also controversy in the field about the importance of active surveillance cultures in infection control.

This Master's paper is a systematic review of the effectiveness of active surveillance cultures to decrease hospital-acquired MRSA. National guidelines, existing reviews, and original research will be reviewed, and clinical recommendations from a national health care improvement campaign will be evaluated. Current evidence on the ability of active surveillance cultures to decrease MRSA-related morbidity and mortality, and on the cost-effectiveness of active surveillance culture programs, will be summarized.

History of Methicillin-Resistant Staphylococcus aureus (MRSA)

Drug resistant organisms have been recognized as a problem for decades. In 1943, only four years after penicillin became widely used, the first strains of penicillin resistant Staphylococcus aureus were isolated.[3] Resistant bacteria were able to produce penicillinase, an

enzyme that renders that antibiotic inactive. Since that time, bacteria have continued to evolve ways to evade the action of penicillin and over 200 types of penicillinases have been discovered.[4] As the bacteria have evolved, there have also been advances in the pharmacology of antibiotics that have allowed physicians and infection control officers to maintain effective infection treatment and control. An example of one such advance in 1960 is methicillin; however, like its older counterpart, penicillin, Staphylococcus aureus soon developed resistance to the drug. The first isolates of methicillin-resistant Staphylococcus aureus (MRSA) were discovered in the United Kingdom just six months after the introduction of the drug.[5] The first cases of MRSA in the United States occurred in 1968.[2] Thirty years later, in 1999, slightly over 50% of the Staphylococcus aureus isolates taken from patients in intensive care units (ICUs) in the United States were resistant to methicillin.[2] The resistance problem has continued to grow and now over 60% of ICU patients with Staphylococcus aureus have MRSA.[2] (Figure 1)

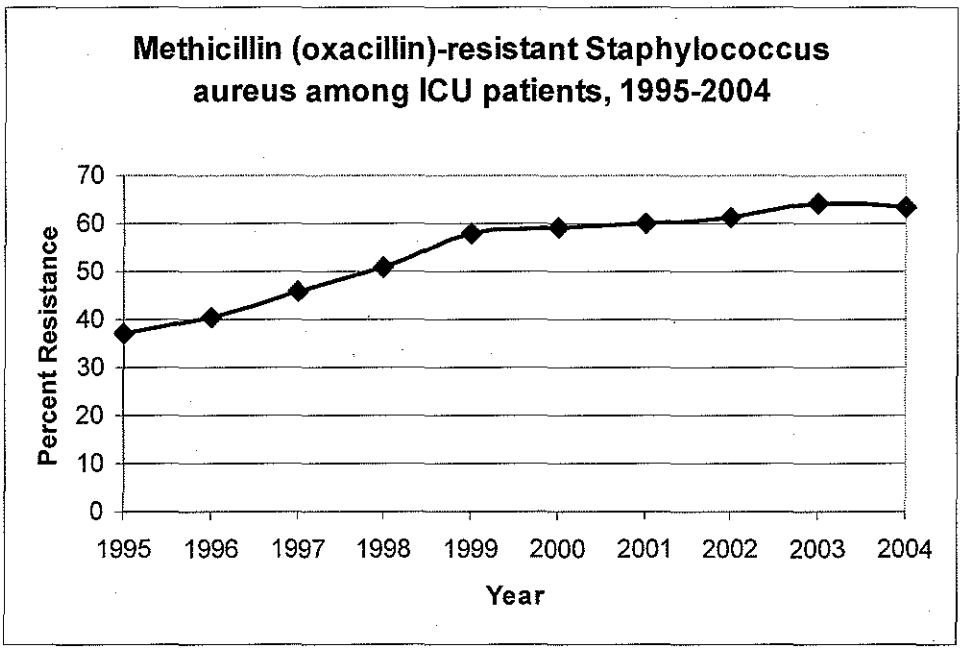

Figure 1. Methicillin-resistant strains of Staphylococcus aureus have increased in the United States over the last 12 years. Source: National Nosocomial Infections Surveillance (NNIS) System.[6]

Researchers have been able to determine that methicillin-sensitive Staphylococcal aureus (MSSA) becomes resistant when it acquires a large genetic element called staphylococcal cassette chromosome *mec* (SCC*mec*).[4] Genetic analysis of MRSA isolates from a variety of locations throughout the world indicate that SCC*mec* has only been transferred from a MRSA strain to a MSSA strain a few times; therefore, worldwide, there are only a few clonal types of MRSA.[4,5] This implies that MRSA does not evolve from random de novo mutations within an individual colonized with MSSA.[4] Instead, patients with MRSA colonization or infection most likely have acquired it from coming into contact with drug resistant bacteria. Therefore, preventing MRSA exposure and transmission are key in the control of the drug resistant organism.

Nosocomial Infections: A Public Health Problem

As a combined group, infectious diseases are the third leading cause of death in adults in the United States behind heart disease and cancer.[4] Unfortunately, a percentage of these infections are acquired in hospitals. Infections are considered to be hospital-acquired, or nosocomial, if they appear after two days of hospitalization or within thirty days after discharge.[7] Excluding other types of healthcare facilities, in hospitals alone there are approximately 2 million nosocomial infections per year in the United States.[8] Because many hospital-acquired infections emerge as complications of an underlying disorder or procedure, it is hard to determine exactly how much morbidity and mortality they cause; however, it is clear that the presence of microorganisms in hospitals does contribute to overall increases in morbidity, mortality, and healthcare costs.[5] One estimate suggests that nosocomial infections could be responsible for 90,000 deaths per year in the United States.[8]

MRSA Control Measures

As a nosocomial or hospital-acquired infection, MRSA presents a significant burden to the United States healthcare system. Although it is now possible to be infected with community-acquired strains of MRSA, the majority of MRSA infections are still acquired in healthcare facilities. Accordingly, there have been many attempted interventions to reduce MRSA infection rates. To spread an infection, there must be 1) a source, 2) a mode of transmission, and 3) a susceptible new host. In hospitals, it is difficult to control source populations and susceptible new hosts, so most infection control measures are aimed at interrupting the transmission of pathogens.[9]

Thorough hand washing is commonly cited as the most important intervention for controlling spread of infection from one patient to another.[9] In addition to hand washing, the Centers for Disease Control and Prevention (CDC) also recommends that patients infected with certain microorganisms are assigned to a single room, transported as infrequently as possible, and have specific or individualized patient care equipment available in the room.[9] In certain cases, gloves, protective gowns, and masks may be required.[9]

The Hospital Infection Control Practices Advisory Committee (HICPAC), in conjunction with the CDC, have also defined two tiers of isolation precautions to prevent the transmission of microorganisms.[9] The first tier is called "standard precautions" and it applies to all hospitalized patients and includes using gloves and/or other effective barriers when handling blood, bodily secretions, mucous membranes, or nonintact skin. The second tier is called transmission-based precautions and it includes three divisions: airborne precautions, droplet precautions, and contact precautions. These transmission-based precautions are used for patients who have a documented

infection.[9] MRSA is primarily spread through direct or indirect contact, so patients infected with MRSA must be placed on contact precautions.[9] When a patient is on contact precautions, anyone interacting with the patient must use patient-specific equipment if possible and wear protective gowns and gloves. Masks or respiratory barriers are not needed.[9]

In 2003, the Society for Healthcare Epidemiology of America (SHEA) published a special report titled "SHEA Guideline for Preventing Nosocomial Transmission of Multidrug-Resistant Strains of Staphylococcus aureus and Enterococcus."[4] The guideline was commissioned because the organization felt it was not making progress with reducing the number of hospital-acquired infections despite it being a priority.[4] The recommendations put forth in the SHEA guideline were not based on a systematic review.
Instead, recommendations stemmed from evidence found in literature published on PubMed MEDLINE (1966-2002, unreported search strategy) and unpublished literature in the authors' libraries. The major recommendations of the guideline involve using active surveillance cultures to identify the reservoir from which MRSA can spread, limiting unnecessary antibiotic use to reduce the risk of more bacteria developing drug resistance, and increasing hand hygiene, barrier precautions, and decolonization of colonized patients to limit opportunities for transmission.[4]

The 2003 SHEA guideline was the first time that a major infection control organization strongly recommended the use of active surveillance cultures and it created controversy within the field.[10] Despite the controversy, other groups and policy makers seemed to take interest in active surveillance cultures as a new approach to improving infection control. One such organization is the Institute for Healthcare Improvement (IHI).

Institute for Healthcare Improvement: *The 5 Million Lives Campaign*

The IHI is a non-profit organization that was founded in 1991 to "improve the lives of patients, the health of communities, and the joy of the healthcare workforce."[11] The IHI launched the *5 Million Lives Campaign* in December 2006 with a mission to "protect patients from five million incidents of medical harm over the next two years [Dec 2006 – Dec 2008]."[12] The organization defines medical harm as:

> "Unintended physical injury resulting from or contributed to by medical care (including the absence of indicated medical treatment), that requires additional monitoring, treatment or hospitalization, or that results in death. Such injury is considered harm whether or not it is considered preventable, resulted from a medical error, or occurred within a hospital."[12]

In order to substantially reduce medical harm, the campaign managers hope to enlist 4,000 hospitals in the United States to work on quality improvement in eleven different focus areas. These focus areas are: improve rapid response teams, provide evidence-based care for acute myocardial infarction, provide evidence-based care for congestive heart failure, prevent adverse drug events, prevent harm from high-alert medications, reduce surgical complications, prevent pressure ulcers, prevent central line infections, prevent surgical site infections, prevent ventilator associated pneumonia, and reduce MRSA infection rates.[12]

Many of the *5 Million Lives Campaign's* goals are concentrated on the morbidity and mortality related to nosocomial infections. Of their infection control goals, reducing MRSA infection rates may be one of the most significant because MRSA is often the bacterium isolated from central line infections, surgical site infections, and ventilator associated pneumonia. By achieving the goal of MRSA infection reduction, it is likely that it will be easier to meet other

infection-specific goals. The IHI recommends using a five-pronged approach to reduce MRSA infections that includes:

1. Hand hygiene
2. Active surveillance cultures
3. Isolation precautions
4. Improved environmental services cleaning
5. Ventilator and central line bundling

Active surveillance cultures are the focus of this Master's Paper since this intervention is relatively new, controversial, and not conclusively shown to be successful or cost-effective over time.

Active Surveillance Cultures (ASCs)

Colonized and infected patients, not environmental contamination, represent the largest reservoir of MRSA in health-care facilities.[5, 13] At many institutions, only patients with infection-like symptoms have microbiological samples taken to be cultured to assist with the diagnosis of active MRSA infection. While this effectively identifies infected patients who need immediate treatment, it does not address asymptomatic, colonized patients who represent the other portion of the pathogen reservoir. It has been estimated that 35-84% of colonized patients go undetected by clinical culturing of only symptomatic patients.[5] Using active surveillance cultures (ASCs), or universally screening all patients admitted to a unit by culturing microbiological samples taken from the anterior nares, will identify 80% of patients colonized with MRSA.[5]

Identifying all of the colonized patients is only the first step in eliminating the reservoir of MRSA. The knowledge gained from active surveillance cultures is only helpful in reducing cross contamination if it helps hospital staff use appropriate contact and hygiene measures. As

MRSA carriers are identified, they can be treated in a manner similar to other patients with active MRSA infections. By isolating colonized patients and putting them on contact precautions, health care workers *theoretically* will be more likely to adhere to strict hygiene measures and less likely to spread the infection to other patients. Further, colonized patients can be decolonized to eradicate the MRSA with a fairly simple treatment regimen involving chlorhexidine gluconate for washing, topical intranasal mupirocin, and/or oral rifampin and doxycycline for seven days.[14]

Although identifying patients who act as a reservoir of MRSA and then managing them accordingly intuitively seems like a good idea, there is a great amount of controversy surrounding the concept of active surveillance cultures. A survey of 463 infectious disease specialists indicates that there is little agreement on the subject.[15] The study showed that only 50% of the specialists were in favor of using active surveillance cultures (ASCs), and only 30% worked in healthcare facilities that routinely used ASCs. The half of the respondents who oppose universal MRSA screening cite the following reasons:

> "First, need additional laboratory resources and are costly; second, create increased demand for isolation rooms; third, could cause logistic difficulties when newly identified patients are moved from one room to another; and fourth, could delay placement of some patients into extended-care facilities. Additionally, the effectiveness of screening cultures to reduce transmission of MRSA has not been established in randomised trials."[15]

To further complicate matters, there is not a standard definition of what constitutes an "active surveillance culture." It is unclear what population should be screened for MRSA colonization. Possible options would be to screen all patients admitted to the hospital or only "high-risk" patients, which could include patients being readmitted, admitted to an ICU, or transferred from another hospital or long term care facility as well as patients with certain

medical conditions. It is also unclear how isolation precautions should be used in conjunction with ASCs. One option is that all of the patients in the chosen screening population should be put on isolation precautions until it is proven that they are negative for MRSA, but another option is that patients should they be put on precautions only after it is shown that they are positive for MRSA. The frequency of screening is not defined either, and there does not appear to be much understanding of how soon after admission a previously negative patient can become colonized and how often follow up cultures should be performed to expeditiously identify these newly converted patients.

SHEA and the IHI, among other professional organizations, actively support ASCs as a part of their campaign to eliminate MRSA infections; however, hospitals have been left to decide for themselves exactly what should be done and how ASCs should be incorporated into their infection control protocols.

Focused question

Professional organizations and infection control officers agree that hospital-acquired infections must be prevented, but do not agree on the most effective method of prevention. In adult medical and surgical intensive care units, are active surveillance cultures (compared to no screening cultures or usual care) associated with MRSA-related mortality, incidence of MRSA infections (bacteremia, cellulitis, abscess), or cost of MRSA-related care?

METHODS

Defining the question

Population = patients in adult surgical or medical intensive care units

Intervention = active surveillance culture

Comparison = no surveillance cultures or usual care (ie, screening only high-risk patients)

Outcome = MRSA-related mortality, incidence of MRSA infections, cost of MRSA-related care

This systematic review addresses only patients in intensive care units because these units have been shown to be the most likely location for the cross transmission and acquisition of nosocomial infections that are resistant antimicrobial drugs.[16] The intervention to be evaluated is nasal swabs for culture of MRSA that occur at admission to the ICU and at least weekly thereafter because nasal swabs alone have been shown to identify 80% of MRSA carriers, which is more than any other body site.[12] However, studies that collect culture specimens from other body sites in addition to the anterior nares at least weekly will also be included. The comparison group is defined as a group that does not receive weekly cultures from the nares for MRSA detection or a group that receives usual care (ie, comparison of screening only high-risk patients vs. universal screening). The outcomes are limited to MRSA-related mortality, incidence of MRSA infections, and cost of MRSA-related care.

Search strategy

To maximize the sensitivity of the search, articles were gathered from a wide variety of sources. The following search strategies were used in PubMed MEDLINE (1966 - present), Web of Science (1955 - present), CINAHL (1982 - present), and the Cochrane Library:

("Methicillin Resistance"[Majr] OR "methicillin resistant"[tw] OR "methicillin resistance"[tw]) AND ("Staphylococcal Infections"[Majr] OR "Staphylococcus aureus"[Majr] OR (mrsa[tw] NOT medline[sb])) AND ("sentinel surveillance"[mesh] OR surveillance[tw] OR "Mass Screening"[mesh] OR screening[tw] OR active screening[tw] OR active surveillance[tw])

("Methicillin Resistance"[Majr] OR "methicillin resistant"[tw] OR "methicillin resistance"[tw]) AND ("Staphylococcal Infections"[Majr] OR "Staphylococcus aureus"[Majr] OR (mrsa[tw] NOT medline[sb])) AND ("economics"[Subheading] OR "costs and cost analysis"[MeSH Terms] OR cost[Text Word])

List of search terms:

1. methicillin resistance
2. methicillin resistant
3. Staphylococcal infections
4. Staphylococcus aureus
5. MRSA
6. sentinel surveillance
7. surveillance
8. mass screening
9. screening
10. active screening
11. active surveillance
12. economics
13. costs and cost analysis
14. cost

Also, a hand search of the Centers for Disease Control and Prevention and Institute for Healthcare Improvement websites was completed to look for guidelines and cited original articles. Six of the major journals in the field of infection control were also hand searched from 2000-2007. These journals are Journal of Infectious Disease, Clinical Infectious Diseases, Journal of Hospital Infection, Infection Control and Hospital Epidemiology, and the American Journal of Infection Control. Finally, the reference lists of included articles were hand searched.

Personal communication with David Weber, MD, MPH, an expert in the field of hospital infection control, confirmed the inclusiveness of the overall search strategy.[17]

Eligibility criteria

The study population was limited to patients in intensive care units who were screened for MRSA at admission and at least weekly thereafter. After an exploratory search of the

literature, these parameters seemed to be the most commonly used and have a certain degree of scientific reasoning behind them.[12, 16, 18] Further, the primary outcomes chosen were patient centered (ie, MRSA infection rates, MRSA-related mortality, or all cause mortality) or related to cost-benefit.

The body of literature regarding active surveillance cultures includes few studies with rigorous study designs; therefore, broad criteria for study designs that could be included were set. More emphasis was placed on studies that were well designed with appropriate control groups, but uncontrolled before-and-after studies and ecological studies were also included to cover the literature upon which current recommendations have been made (Table 1).

Table 1. Eligibility criteria.

Inclusion Criteria	Exclusion Criteria
Adult medical or surgical ICU patients	All non-ICU patients, and all Neonatal ICU or Pediatric ICU patients
Measurement of hospital-acquired drug resistant Staphylococcal aureus (including methicillin, oxacillin, etc)	Measurement of community-acquired S. aureus or pathogens other than S. aureus
At least weekly nasopharyngeal cultures from all ICU patients in intervention group	Less frequent or unscheduled nasopharyngeal cultures or culturing only targeted patients
Comparison group similar to intervention group, but not receiving screening nasopharyngeal cultures	Lack of a comparison group or control group
Primary outcomes: MRSA-related mortality, infection, or costs	Primary outcomes unrelated to MRSA patient outcomes or costs
Experimental study design (ie, RCT), quasi-experimental design (ie, nonrandomized trial), controlled observational design (ie, cohort studies, case-control studies, time series), uncontrolled before and after study design, or ecological studies	Cross sectional studies, case series, case reports, expert opinion, reviews
English language	Non-English language

Selection of eligible articles

First, the titles and abstracts generated by searching were subjected to the inclusion/exclusion criteria. Any article with an abstract that failed to meet any inclusion criteria or that was clearly out of the scope of the review question was excluded. The articles with abstracts that fully or partially fulfilled the inclusion criteria were saved and their full text copies were obtained. The inclusion/exclusion criteria were applied again, this time to the full text articles. In order to be selected, studies had to fulfill all of the inclusion criteria and none of the exclusion criteria.

The judgments about which studies to include were made first by the author. Next, a second reviewer repeated the process starting with the abstracts and then using the full text articles, to reapply the inclusion/exclusion criteria to all of the articles excluded by the author. Any disagreements were resolved by discussion or by using a third reviewer.

The initial search yielded 2578 articles. Either on the basis of title/abstract or full text review, there were 2558 articles that did not meet all inclusion criteria and were excluded from the review. Twenty articles were included in the review. A full QUORUM tree illustrates the process used to arrive at the studies finally included (Figure 2).

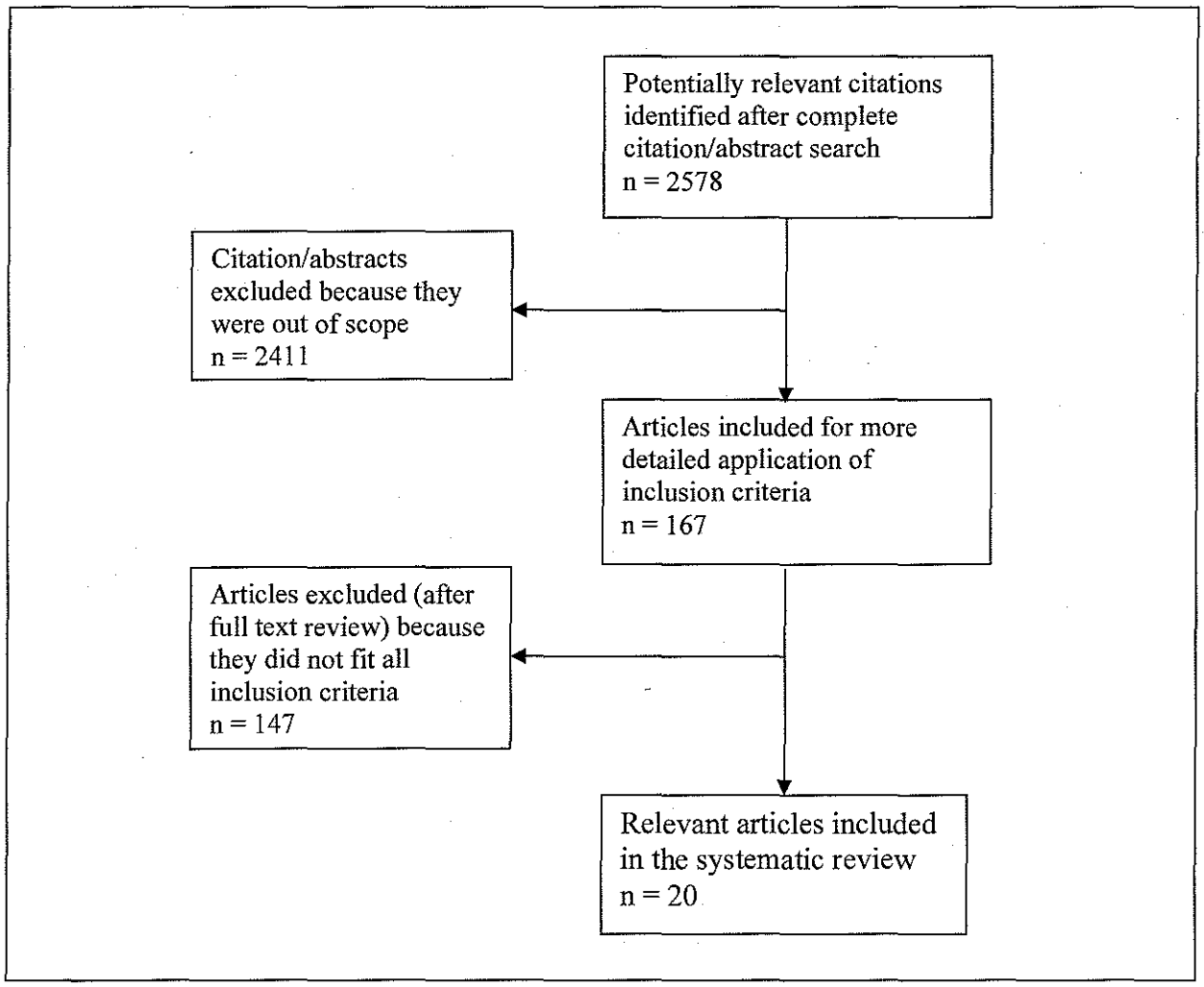

Figure 2. QUORUM tree of articles selected for systematic review.

Quality Assessment and Validity

The quality criteria used to assess the internal validity of each of the included observational studies were based on the guidelines set forth by the United Kingdom's National Health Service Centre of Reviews and Dissemination (Appendix A).[19] Each study was evaluated in terms of the research question(s), description of source and study population characteristics, intervention integrity, data collection and measurement, and analysis methods including adequacy of sample size and statistical methods. It is important to note that specific outcomes and the magnitude of effect of the intervention are separate issues from the quality of the data, and are not included in the quality assessment of each study.

The quality of the economic analyses was rated based on guidelines from the United States Preventive Services Task Force (Appendix A).[20] Each study was evaluated in terms of the research question, appropriateness of the study population and the reference comparison, quality of the effectiveness evidence on which the cost analysis is based, method used to estimate costs, consideration of societal costs, long term costs, and the cost of harms, and statistical methods.

A checklist of items for each type of study design was created and used to rate the internal validity (ie, case selection, measurement, confounding, and statistical analyses) and external validity (ie, study population, interventions, and outcomes). The overall rating of methodological quality was based on consideration of study design, and the internal and external validity assessments. The quality assessment was performed by one reviewer who was not masked to the names of the authors, institutions, or journals.

Observational studies that used control groups and economic analyses could be rated as high, moderate, or low based on the quality criteria checklist that corresponded to their study designs. It is mandatory that highly ranked observational studies have a control group.

Controlled observational studies or economic analysis that satisfied 80% of the criteria on the checklist were rated "high", studies that satisfied 40-79% of the criteria were rated "moderate", and studies satisfying fewer than 40% of the criteria were rated "low".

The same quality criteria checklists were applied to each of the uncontrolled studies in the same manner as the controlled studies, but the scoring system was slightly different. Observational studies that did not have control groups, even if well done, could not be rated as "high" because uncontrolled studies are subject too many possible threats to validity. Therefore, uncontrolled observational studies satisfying 80% of the criteria were rated "moderate" and studies satisfying fewer than 80% of the criteria were rated "low".

Data Abstraction

Studies that met all inclusion criteria were summarized and organized into an evidence table. All data were organized according to methodological quality rating and publication year with the economic analyses in a separate group at the end. The endemic level and/or importation rate of MRSA in the hospitals at which the studies were being carried out were also considered. Although this paper does not focus on the method of culturing the samples taken for ASC, the use of rapid PCR versus standard culturing techniques was noted because methods vary greatly between hospitals and time lag before MRSA identification has implications for the use of isolation precautions and chance of cross-contamination. The categories in the evidence tables are: author and year, study design, location, sample characteristics (including prevalence of endemic MRSA), intervention (including use of PCR), summary of results, and evidence rating (Appendix B).

RESULTS

Twenty studies that examined active surveillance cultures and incidence of hospital-acquired MRSA or MRSA associated costs fulfilled the criteria to be included in this systematic review. There were no randomized controlled trials that include patient-related outcomes of ASCs. Only two out of sixteen observational studies (12.5%) had a control group. There was one retrospective cohort study, one case-control study with a cost-effectiveness analysis, five interrupted time series studies, four uncontrolled before and after studies (one of which included a cost effectiveness analysis), five ecological studies, and four economic analyses.

None of the studies included in this systematic review were of high quality. The two controlled studies had the best internal validity; however, they were still limited by weak study designs and other threats to validity. The maximum rating that uncontrolled studies could obtain was moderate due to the inherent weaknesses in the study designs. Three of the five interrupted time series were well done considering the limitations of the study design and got a moderate quality rating. All of the before and after studies and ecological studies were of low quality (Table 2).

Table 2. Methodological quality by study design.

Study Design	High Quality, n	Moderate Quality, n	Low Quality, n
Retrospective Cohort Study	--	**1**[21]	--
Case-Control Study	--	**1**[22]	--
Economic Analysis	--	**2**[23, 24]	**2**[25, 26]
Interrupted Time Series Study	--	**3**[27-29]	**2**[30, 31]
Before and After Study	--	--	4[32-35]
Descriptive/Ecological Study	--	--	5[36-40]

A summary of all included studies can be found in an evidence table (Appendix B). Specific information highlighting significant results and the critical appraisal of the included studies follows.

Chaix and colleagues did a case-control study in 1999, which is an observational study that warrants considerable attention in this systematic review because it is one of the only studies with a control group and it met most methodological standards.[22] The cases and controls were selected properly and were comparable with respect to identified possible confounders, the intervention and measurement of outcomes was the same in both groups, and there was an appropriate statistical analysis. However, case-control studies are subject to considerable confounding, which threatens the overall internal validity and is the primary reason for the "moderate" quality rating. The cases in this study were adult medical ICU patients with MRSA infections who were randomly selected from an infection control database, and the matched controls were medical ICU patients who did not acquire MRSA. Over a four year period in their hospital, MRSA infection incidence decreased from 5.6 to 1.4 cases per 100 admissions. They also calculated that an ASC program is cost-effective if MRSA importation rates are between 1% and 7%.[22]

The three interrupted time series of moderate quality were all in agreement that an ASC program will decrease the incidence of hospital-acquired MRSA infections. Huang *et al* reported the most striking results; a 75% decrease in MRSA infections in the ICU where the ASC program was being used, and a 40% decrease in MRSA infections in the remainder of the hospital that was not receiving the intervention.[29] Wernitz *et al* report a 48% decrease in infection incidence, and Gould *et al* report an 11% decrease.[28, 41] Despite the limitations of the

study design, all three of these studies were well done and their results should be seriously considered. They each included good measurements of baseline characteristics, evidence that the ASC intervention was independent of other interventions, discussion of possible confounders, comparisons to secular trends, and other appropriate statistical analysis.

Three of the four economic evaluations agree that some form of ASCs and the subsequent management of colonized patients are cost effective. But, only two analyses, Wernitz *et al* and Lucet *et al*, are true cost-benefit analyses with reasonable internal validity and study designs.[23, 24] These two studies identified all relevant costs and valued them appropriately, included comparisons to alternative interventions, and performed a sensitivity analysis. The primary weakness in both studies is that they base their effectiveness evaluations on trials they have performed rather than on a collection of the best available evidence. Lucet *et al* performed a cost effectiveness analysis based upon a multicenter ecological study. The analysis by Wernitz *et al* is based upon an interrupted time series study, and is the best cost-effectiveness evidence included in this study.

Wernitz *et al* reported in 2005 that their hospital was only compensated for 26% of costs required to care for MRSA patients who exceeded their diagnosis related group (DRG) length of stay and payment threshold value as a result of a MRSA infection. Using a high-risk screening program in their hospital, they were able to prevent about 35 cases of MRSA infection, including surgical site infections, pneumonia, and blood stream infections, and estimated that their program saved the hospital 110,236 euros annually.[23] The uncompensated costs of caring for MRSA patients was high (8044 euros per patient), and they calculated that only three cases of MRSA infection have to be prevented each year in order to make an ASC program for high-risk patients cost-effective.[23]

Lucet and colleagues were the only group who studied the costs of universal screening of all patients admitted to an ICU.[24] In their cost-benefit analysis of moderate quality, they strongly support universal ASCs as they found using high-risk profiles for selective screening not sensitive enough to detect enough MRSA cases, and that universal screening was the most beneficial and cost-effective in their hospital. Using a sensitivity analysis, the determined that universal screening and preventive isolation saved money when the prevalence of MRSA colonization was between 2% and 20%.[24]

The other two economic evaluations were cost comparison studies and received low quality ratings. Cost comparison studies are weak because they only assess the cost and not the effectiveness of an intervention.[19] Neither of the following studies are fatally flawed because they did include most relevant costs and valued them appropriately; however, there is no consideration of alternative interventions, no measure of effectiveness, and no sensitivity analysis.

Gavaldà and colleagues used a cost comparison between the costs of a high-risk screening program and the attributable costs of MRSA infections. Similar to the findings by Wernitz *et al*, they reported that a high-risk screening program is cost effective if four MRSA cases are prevented. In their hospital, that meant reducing incidence of infections by 11%.[26]

The fourth economic study, a cost comparison by Kim *et al* in 2001, was in disagreement with the others. They were wary of recommending ASCs because they found that screening and the subsequent management of colonized patients accounted for 45% of the total MRSA-related costs in their hospital.[25]

The remainder of the included observational studies also have low internal validity, and their results should not contribute greatly to the conclusions drawn from this review. Seven of

the ten low quality studies are in agreement with the relatively higher quality studies mentioned above, and state that ASCs are effective in reducing the number of hospital-acquired MRSA infections. Eveillard and colleagues only found a decrease from 10% to 9% acquisition of MRSA per 100 days with ASC of ICU patients only.[32] But, when they included ICU patients, other high-risk patients, and an alert system in the intervention there was an overall 58% decrease in MRSA infections from 10.4% to 3.1% MRSA acquisition per 100 hospitalization days of MRSA carriers.[32] The articles by Shitrit *et al*, Pan *et al*, and Souweine *et al* all report about a 50% decrease in MRSA infection incidence.[30, 33, 35] Souweine and collegues also report that although infection rate decreased with the ASCs, there was no change in the rate of MRSA-related mortality.[35] Tomic *et al* report a dramatic decrease in incidence of MRSA infections from 4.0 to 0.4 cases per 1000 patient-days (50% to 6.1% acquisition).[34] Lucet and colleagues report a more moderate decrease from a 7.0% to a 2.8% MRSA infection incidence.[37] Troche and colleagues found an initial decline in MRSA infection incidence from 9.2 to 6.6 cases per 1000 patient-days, but then ASC compliance dropped to only 68% and the infection rate increased to 11.6 cases per 1000 patient-days. By the end of the study period, compliance had improved and there was a decrease in MRSA acquisition rate to 5.6 cases per 1000 patient-days.[39]

Three low quality studies report negative findings. The study by West and colleagues included two hospitals.[31] In one hospital, the incidence of MRSA infections decreased from 0.76 to 0.45 cases per 1000 admissions. However, at the other hospital, there was no change in the infection rate after implementing ASCs.[31] Thompson *et al* also report negative findings and do not support ASCs because the incidence of MRSA infections remained 5% over the course of their study.[40] Nijssen *et al* specifically separated the surveillance cultures from other subsequent

patient management like contact isolations, and performed daily ASCs on patients an adult medical ICU without reporting the results to hospital staff or using isolation.[38] Over a three month period, the mean daily prevalence of MRSA was about 10%, which did not show a changing trend for MRSA colonization or infection compared to a three year period surrounding the study. Further, there was no cross-contamination of MSSA or MRSA between ICU patients, and the authors conclude that had the ASC program been followed up with isolation precautions they would have appeared falsely successful and are not a useful infection control strategy.[38]

The results of the poor quality studies may be used to support results from better studies; however, without a control group, or at least trend data that have been statistically adjusted for serial autocorrelation and secular trends, all of the low quality studies are at risk for contamination of the intervention, measurement bias, and confounding. The threats to validity and poor evidence give very little scientific basis for drawing conclusions and making recommendations.[42]

DISCUSSION

Based on the five moderate quality observational studies and the two cost-benefit analyses, the results show that ASCs are associated with a decreased incidence of hospital-acquired MRSA infections and that ASCs are cost-effective under a wide variety of conditions. However, the lack of high quality evidence and predominance of generally mediocre studies must be taken into account and may introduce doubt to the overall positive results.

Concerns about study design and confounders

There were only two studies with control groups found in the literature. These studies were done well and have few threats to their validity. Their results should be emphasized over the results of the remaining fourteen uncontrolled observational studies included in this systematic review. However, although these two were the best methodologically in this review, prospective cohorts and randomized controlled trials are significantly stronger and more valid study designs.[42] Unfortunately, most of the studies in this review and those that have also been used as evidence for guidelines are subject to confounding and have other problems inherent to their study designs.

Only two of the articles reported using a control group,[21, 22] and none of the studies used randomly assigned controls, so the possibility of confounding is great. A few potential confounders could be compliance with taking swabs for culture, compliance with isolation precautions, length of time before culture results are reported, patient length of stay, patient case mix, staffing levels and staff workload, use of prophylactic antibiotics, and the endemic level of community-acquired MRSA colonization and infection.

Ecological study designs are fraught with weaknesses. The ecological studies included in this review analyzed a population at different points in time once the ASC intervention was started.[36-40] The unit of analysis is the population of patients, not the individual; therefore, ecological studies lack the necessary linkage between individual patients and outcomes. This potential threat to the validity is termed "ecological fallacy," which is defined as incorrectly assuming that relationships found in aggregate data will also be found among individuals.[43] Additionally, without a control group for comparison, it is impossible to determine whether the measured outcomes are associated with or caused by the intervention. Ecological studies are of low quality and any conclusions drawn from them must be critically appraised and considered with great reservation.

Uncontrolled before and after studies can be effective for demonstrating a change in the incidence rate of the outcomes, but without a control group or at least trend data (as used in interrupted time series) it is impossible to tell if the intervention caused the observed change. Although statistical significance tests can be applied to help rule out random chance causing the change in outcomes, there are still many confounders that could be present in the before or after period that cause differential bias and effect the results. Large differences in outcomes between the pre- and post-intervention periods may be indicative of some effect, but there cannot be certainty in the conclusions drawn from this kind of evidence.

Additionally, in uncontrolled before and after studies, when a hospital unit starts the intervention and begins actively screening for MRSA, the detection rate increases; therefore, the apparent MRSA prevalence increases although true prevalence remains the same initially. The number of MRSA cases cannot be used as a common denominator to compare the frequency of MRSA colonization before and after the intervention, so it is impossible to know how the

pathogen reservoir and endemic level of MRSA are changing. However, it is still possible to measure and compare the incidence of overt MRSA infections as long as the diagnoses are made from clinical cultures and constellations of symptoms rather than the active surveillance cultures in the study intervention.

The Role of a Randomized, Controlled Trial (RCT)

Many infection control specialists, epidemiologists, and methodologists have called for a randomized controlled trial (RCT) in order to obtain reliable results and stronger guidance.[44] It is possible that a large, multicenter RCT that uses hospitals as the unit of analysis could be very useful in answering many questions regarding the effectiveness of ASCs in infection control. If the RCT demonstrates a positive relationship and confirms the results from the weaker studies discussed above, then the next steps are clear. As suggested by the SHEA guideline, the hospital infection control departments will begin to implement some version of ASCs in their ICUs and other high-risk units. The result will potentially be a reduction in the MRSA infection rates and decreased levels of preventable morbidity and mortality.

However, if the RCT has a negative result and finds that ASCs do not cause a decrease in MRSA-related morbidity, mortality, and costs, the steps to be taken will not be so obvious. Do the results of one highly valid study outweigh the results of many less valid studies? It is unclear what would happen in this situation, but it is likely that the controversy would become more heated. Many who have been calling for an RCT will feel justified in not implementing ASCs. Conversely, groups like SHEA and IHI who have already supported and recommended ASCs will likely continue to do so, citing the preponderance of observational data showing a positive relationship.

The Scandinavian Experience

Many Scandinavian countries have been using ASCs and isolation for a number of years and they may be able to serve as a model in the absence of high quality studies or an RCT. The prevalence of MRSA in Scandinavian countries is very low at only about 2%.[45] Even more notably, the prevalence of MRSA in the Netherlands has been as low as 0.5% in 1999.[46] The Dutch attribute this infection control success to their "search and destroy" method.

The Dutch Working Party Infection Prevention sets the guidelines for the control of MRSA in Dutch hospitals and it is largely centered on "search and destroy." All patients transferred from an outside facility are kept in quarantine in a single room with a negative pressure anteroom for at least two days until three serial cultures are negative for MRSA. Cultures are taken at one hour intervals after admission from the nose, throat, perineum, urine, sputum, and open wounds. All other patients directly admitted to the hospital are also screened serially three times at all of the sites mentioned above, but are not initially isolated. If one of these patients is colonized with MRSA, then they are moved to an isolation room. All other patients in the same original room must also be screened and put into isolation until it is proven that they are MRSA negative. Any involved health care workers are screened daily for MRSA. When two patients or one health care worker harboring MRSA is detected, the unit is closed to new admissions until the colonization/infection is treated.[46]

Many European countries use active surveillance cultures and subsequent isolation to control MRSA cross-contamination; however, the above described method from the Netherlands is the most aggressive.[46] It is unclear if such rigid treatment of patients and health care workers in the United States would be acceptable.

Additionally, it is unclear if the costs of a strict "search and destroy" program to the health care system and society in America would be acceptable or affordable. The University Medical Center Utrecht in the Netherlands retrospectively analyzed the costs of their "search and destroy" program over a ten year period from 1991 to 2000.[47] Included in the study were costs associated with additional disposable materials, cultures, medication, decontamination of exposed items, and unit closures. Over the last decade, their "search and destroy" program cost about 2.8 million euros.[47] Included in that value is the cost of 2,265 lost hospitalization days and 48 unit closures. Health care delivery and payment schemes are different in the United States and the Netherlands. The United States is also much larger and has many more hospitals and ICUs than the Netherlands. Setting the material costs aside, it is possible that losing thousands of hospital days across all of the hospitals in the United States could be overwhelming to health care financing.

Remaining Concerns: Target Population for Screening

Most of the included studies used high-risk groups to target their screening programs, but others used universal screening of all patients admitted to certain units. It is unclear what population should be screened. For example, Huang *et al* showed that using ASCs to reduce the number of MRSA infections among ICU patients actually reduced the MRSA infection rate in the remaining units of the hospital, which seems to indicate that targeted screening is sufficient.[29] However, Lucet *et al* state in their hospital "only universal screening detected MRSA carriage with acceptable sensitivity."[24]

If it is determined that selective screening of high-risk patients is sufficient, then there must be a good definition of "high-risk." Warren *et al* published an epidemiological study

characterizing independent risk factors associated with MRSA colonization in patients admitted to a surgical ICU.[18] Of the 1,469 patients screened over a fifteen month period, 8% had nasal MRSA colonization. Risk factors for MRSA colonization at admission to the ICU included:

1. Hospitalization in the past year
   - 1-2 admissions = aOR 2.60, 95%CI 1.47-4.60
   - >2 admissions = aOR 3.56, 95%CI 1.72-7.40
2. Hospital stay >5 days prior to ICU admission
   - aOR 2.54, 95%CI 1.49-4.32
3. Chronic obstructive pulmonary disease
   - aOR 2.16, 95%CI 1.17-3.96
4. Diabetes mellitus
   - aOR 1.87, 95%CI 1.10-3.19
5. Isolation of MRSA in past six months
   - aOR 8.18, 95%CI 3.38-19.79[18]

Used as a predictive test to identify patients with MRSA colonization, the presence of at least one of the above independent risk factors had a sensitivity of 89% and a specificity of 45%. The negative predictive value of this risk factor screening tool is 97%.[18] Therefore, a patient without any of the above risk factors can likely be ruled out as a possible MRSA carrier and does not need to have nasal swabs done for a microbiological culture.

Only studies of adult ICU patients were included in this systematic review. Since the endemic levels of MRSA are generally higher in ICUs than other hospital units, this entire group of acute patients could be considered high-risk. However, some of the authors of the articles included in this review only used a high-risk group within the ICU population for their studies assessing the role of ASCs.[26, 28, 34] The three studies that used high-risk ICU subgroups defined patients with a known history of MRSA infection or colonization and patients transferred from nursing homes as high-risk. One study also included patients with more than thirty days of hospitalization in an ICU or surgical ward.[26] Another study included patients transferred from another hospital and patients who had had an operation within the last year.[34] The third study

had the broadest spectrum of high-risk patients and included patients transferred from hospitals where MRSA is endemic and patients requiring dialysis who also have a skin infection, patients receiving treatment that involves any kind of invasive device, and patients with pressure sores.[28]

Remaining Concerns: Laboratory Methods

Currently, there is no standard method for culturing and detecting MRSA across different clinical microbiology labs. Many labs use one of the numerous forms of selective incubation media, others use S. aureus identification tests and a methicillin susceptibility test, and some use direct identification tests via polymerase chain reaction (PCR).[48] Even labs that use the same methods may have different experimental conditions such as the incubation temperature or salt concentration of the culture media.[48] The high level of variability in culturing method, time, and cost makes it difficult to assess each hospital's ability to accommodate increased demand for culturing if ASCs are implemented.

Kunori *et al* developed a cost effectiveness model based in year 1999 English pounds to examine various laboratory screening approaches to detect MRSA.[48] Based on details from a literature search, the British National Health Service costs database, and modeling with sensitivity analysis, they report that the most cost-effective screening method is to inoculate a single nasal sample directly onto ciprofloxacin Baird-Parker agar without the use of broth and then confirm the result with a staphylococcal latex test (ie, Pastorex Staph-Plus), but not with any methicillin-resistance test.[48] This is valuable information for hospitals with labs that are unsure if they can afford an increased volume of MRSA samples for culture.

However, some may argue that there are advantages to using rapid screening with PCR even though the start up costs and the costs of each test are high. Some hospitals may choose to

preemptively isolate patients until it is proven that they are negative for MRSA. With rapid testing, it is possible to rule out patients without MRSA more quickly, so the number of costly isolation days will decrease. More commonly, hospitals using ASCs wait to isolate patients until after they are identified as MRSA carriers. Rapid screening with PCR will reduce lag time by identifying the positive patients who need to be isolated sooner, thereby increasing the effectiveness of the program. Notably, PCR was not used in any of the studies included in this review. The use of PCR for detecting MRSA is relatively rare and still being studied.

Harbarth *et al* used quick, multiplex immunocapture-coupled PCR in the surgical and medical ICUs of their hospital in Switzerland and found that the median time from ICU admission to notification of test results decreased from 87 to 21 hours in the surgical ICU ($p < 0.001$) and from 106 to 23 hours in the medical ICU ($p < 0.001$).[49] The combined use of the quick screening method and preemptive isolation of all patients until a negative result was obtained was able to reduce the number of hospital-acquired MRSA infections in the medical ICU (RR 0.3, 95%CI 0.1-0.7), but not in the surgical ICU (RR 1.0, 95%CI 0.6-1.7).[49] The results of this study are mixed, and it is hard to determine whether implementing PCR screening for MRSA will actually have an effect on patient outcomes in hospitals with different case mixes.

Remaining Concerns: Contact Precautions and the Psychological Effects of Isolation

As previously mentioned, identification of MRSA carriers via ASCs is only a first step in potentially reducing MRSA infections. Depending on the hospital policy, patients are either isolated until it is proven that they are not colonized with MRSA or they are isolated once it has been shown that they are colonized. Either way, as asymptomatic patients are actively sought

out, the MRSA detection rate will increase and a greater number of patients will subsequently be put in isolation on contact precautions at some point during their hospitalization.

Based on the studies included in the review and the descriptions of the "search and destroy" method in Scandinavia, it is also unclear how contact precautions should be used in conjunction with ASCs. Stricter protocols may favor isolating all patients until they are proven negative for MRSA colonization. However, most of the included studies waited to receive the results from the cultures and then isolated the MRSA positive patients. There needs to be further investigation of the necessity of preemptive isolation, the additional costs of extra days on contact precautions, and a hospital's ability to shift to using mainly single rooms if preemptive isolation techniques are used.

In addition to the increased financial burden to the hospital that comes with higher number of patients on isolation precautions, there are also patient-centered "costs" to isolation. Kirkland and Weinstein at Duke University report from a prospective observational study that health care workers treating ICU patients on contact precautions were about two times less likely to enter the room compared to health care workers taking care of ICU patients not on contact precautions.[50] Evans *et al* from University of Virginia report similar results. They found that isolated patients were visited 5.3 times/hour compared to 10.9 visits/hour for nonisolated patients ($p<0.001$).[51] Additionally, despite more severe disease as designated by higher mean Acute Physiology and Chronic Health Evaluation II (APACHE II) scores among isolated patients (10.1 ± 1.0 vs 7.6 ± 0.8, $P = .05$), the overall contact time with health care workers was significantly less (29 ± 5 vs 37 ± 3 min/h, $P = .008$).[51] It is unclear if the reduced level of contact with health care workers has an impact on patient outcomes. However, one small, prospective cohort study

does indicate that even after one week of isolation precautions, adult patients have worsening depression and anxiety symptoms.[52]

Remaining Concerns: Efficacy of Decolonization

There is a systematic review maintained by the Cochrane Collaboration of all of the RCTs published from 1966 to 2003 that compare the effects of topical or systematic antimicrobials versus placebo on nasal and extra-nasal MRSA carriage, adverse events, and incidence of subsequent MRSA infections.[53] The conclusions drawn from the review of the six included randomized controlled trials are:

> "There is insufficient evidence to support use of topical or systemic antimicrobial therapy for eradicating MRSA. There is no demonstrated superiority of either topical or systemic therapy, or of combinations of topical and systemic agents. Potentially serious adverse events can arise from use of systemic agents. Topical or systemic agents can lead to the development of resistance to the antimicrobial agent used for eradication."[53]

Although the literature, including many RCTs, does not support the use of topical or systemic medications for MRSA decolonization, almost half of the included studies used decolonization as part of their intervention program. Although in this case, the literature is sufficient and the results are clear, there is still variation in the use of decolonization as a part of an ASC program that illustrates the amount of uncertainty and confusion surrounding the subject.

Remaining Concerns: Compliance

Few of the studies included in this review reported levels of compliance with performing nasal swabs for the active surveillance of MRSA. It is unclear how thorough the screening must be to detect enough MRSA+ patients to make the program beneficial.

Additionally, the success of ASCs seems to hinge on the resultant actions that are taken such as isolation, contact precautions, and increased hygiene and cleaning that try to reduce the possibility of cross contamination. Unfortunately, healthcare workers' hands are the primary vehicle for cross contamination of patients in healthcare facilities.[2] The 2002 Guideline for Hand Hygiene in Healthcare Settings included a review of thirty-four observational studies from 1981-2000 that report an average of 40% (range 5-81%) compliance with hand hygiene recommendations in health care facilities.[54] One of the theories supporting contact precautions is that healthcare workers will be alerted to the presence of an infectious agent and will take the necessary precautions needed to avoid its spread. However, in an observational study at a large teaching hospital in Canada, the average compliance with all MRSA precautions was only 28%.[55] In particular, compliance with hand hygiene (either using alcohol rub or washing with soap and water) was 35% and the compliance with gowning and gloving was 65%.[55]

An apparent advantage to using ASCs is that colonized patients who represent the reservoir from which MRSA can spread are identified and can be treated appropriately to reduce pathogenic transmission. However, the success of transmission reduction is largely based on the behavior and health care workers since their hands are currently the most common transmission vectors. With such poor levels of hand hygiene and contact precaution compliance, it is not certain that ASCs and contact precautions will be effective as their use becomes widespread across a variety of types of hospitals. It is unclear what level of compliance with hand hygiene and other infection control practices there must be for ASCs to be useful.

Limitations of this review

All of the components of the search were limited to English, which may present some bias as there may be many researchers who do not speak English as a first language and who have published relevant studies in a non-English journal. However, this bias is likely minimal because there are a great number of studies published in English by researchers from non-English speaking countries that have been included in this review.

As with all systematic reviews of published literature, publication bias may be affecting this review. Publication bias is of particular concern in this review because of the large number of poor quality studies. Studies with negative findings, especially those with moderate or poor quality, are not as likely to be published, and it is possible that the preponderance of studies supporting ASCs present a falsely inflated positive evidence base.

Additionally, the quality assessment and data abstraction components of this systematic review were only performed by one reviewer, not two, due to resource constraints.

CONCLUSION

Observational evidence favors the use of ASCs, but the overall quality is so low that definitive, evidence-based recommendations cannot be made. This review identified many gaps within the literature, including a need for a clear definition of ASCs, a clear implementation protocol that includes a defined screening group and laboratory methods, and rigorous economic evaluations. Considering the paucity of high quality information and the uncertainty concerning ASCs, it is not surprising that there is no general consensus about active MRSA screening among infection control experts.

It is surprising that highly respected professional organizations such as SHEA and IHI have strongly recommended using ASCs in their most recent guidelines without having a strong scientific foundation to support them. However, making recommendations for clinical practice often involves issues outside of basic scientific proof. For example, patient or societal expectations, legal concerns, ethical considerations, and the desire to use novel concepts for quality improvement may also be driving the decision to support ASCs. Considering these factors along with the need to reduce a large public health problem, the generally positive results supporting ASCs, and the great success of the "search and destroy" method in Scandinavia, it is understandable that these organizations favor the implementation of MRSA screening in hospitals across the United States.

A randomized, controlled trial to prove the utility of ASCs has been called for, but may not be a good use of limited research funds. Instead, it may be better to accept the imperfect evidence that demonstrates the usefulness of ASCs in reducing MRSA infections and MRSA-related costs, and to focus further research on defining the details (risk assessment, lower-cost rapid culture methods, treatment for colonized patients) for effective ASC implementation.

APPENDIX A

Evidence Rating Criteria for Observational Studies[19]

One point was given for each "yes" answer. Controlled observational studies that meet 80% or more of the criteria are rated as high, 40-79% are rated as moderate, and less than 40% are rated as poor. Studies that do not include a control group cannot be rated "high." Uncontrolled observational studies that meet 80% of the criteria are rated as moderate, and those that meet less than 80% are rated as low.

COHORT STUDY		
Quality Criterion	**Yes**	**No**
Is there sufficient description of the groups and the distribution of prognostic factors?		
Is the intervention sufficiently described?		
Were the groups comparable on all important confounding factors or were appropriate adjustments made?		
Was the outcome assessment masked to exposure status?		
Was the follow-up long enough for outcomes to occur?		
Did a reasonable proportion of the cohort follow-up?		
Were the drop out rates and reason similar across groups?		

CASE-CONTROL STUDY		
Quality Criterion	**Yes**	**No**
Is the case definition explicit?		
Were the controls randomly selected from the source population?		
How comparable are the groups with respect to confounders?		
Was the intervention assessed the same way for both groups?		
Was the response rate well defined?		
Were reasons for non-response similar in both groups?		
Was an appropriate statistical analysis used?		

BEFORE AFTER STUDY		
Quality Criterion	**Yes**	**No**
Are baseline characteristics measured?		
Was there a power calculation?		
Were possible confounders reported?		
Was there good intervention integrity?		
Was there protection against contamination or ascertainment that intervention was independent of other interventions?		
Were outcomes measured appropriately and consistently throughout the study period?		

Evidence Rating Criteria for Economic Analyses[19, 20]

One point was given for each "yes" answer. Studies with 80% or higher are rated as high, 40-79% are rated as moderate, and less than 40% are rated as poor.

COST BENEFIT ANALYSIS		
Quality Criterion	**Yes**	**No**
Is there a well defined question?		
Are all important and relevant costs and outcomes for each alternative identified?		
Is the study conducted from the societal perspective?		
Is the time horizon clinically appropriate and relevant to the study question?		
Are key harms included?		
Is the best available evidence used to estimate effectiveness?		
Are costs and outcomes appropriately valued? (published data, microcosting, author estimate?)		
Do effect measures capture preferences or utilities?		
Are costs and outcomes adjusted for differential timing?		
Are appropriate sensitivity analyses performed?		
Are the results generalizable?		

Appendix B. Evidence Table

Author, Year	Study Design	Location	Sample Characteristics	Intervention	Summary of Results	Evidence Rating
Huang SS, *et al.*[21] 2007	Retrospective cohort	United States	8013 ICU patients in 12 different ICUs	Unreported culturing method. ASCs at admission, then weekly. Contact precautions if MRSA+.	Detection of MRSA infections increased by 30-135% with ASCs. Incidence density increased from a mean of 6.7 to 8.9 cases per 1000 patient-days.	Moderate
Huang SS, *et al.*[29] 2006	Retrospective interrupted time series	United States	12% importation rate into ICU. 6000 ICU patients	Unreported culturing method. ASCs at ICU admission, then weekly.	Decreased incidence of HA-MRSA bacteremia by 75% in ICU and 40% in non-ICU.	Moderate
Gould IM, *et al.*[27] 2006	Interrupted time series	Scotland	ICU patients	Standard culturing method. ASCs at admission, contact precautions if MRSA+. Topical nasal antimicrobial and chlorhexidine baths for MRSA+ and MRSA-.	ASCs, isolation, and decolonization program reduced MRSA incidence by 11.4% (from about 15% to 5%). Screening 11 patients will prevent 1 case of MRSA.	Moderate
Wernitz MH, *et al.*[28] 2005	Interrupted time series	Germany	73, 080 patients admitted to all units	Unreported culturing method. ASCs of high-risk patients at admission. Contact precautions, therapeutic baths from admission until proven MRSA-. Contact precautions and decolonization if MRSA+.	Based on expected trend estimates, HA-MRSA infections decreased 48%.	Moderate
Chaix C, *et al.*[22] 1999	Case-control	France	4% importation rate into ICU. 54 MICU patients with and without MRSA	Unreported culturing method. ASCs at admission, then weekly. Contact precautions if MRSA+.	Decreased incidence of MRSA infection by 14% (5.6 cases to 1.4 cases/100 admissions). Screening is cost effective if prevalence at admission between 1-7%.	Moderate

Author, Year	Study Design	Location	Sample Characteristics	Intervention	Summary of Results	Evidence Rating
Sandri AM, *et al.*[36] 2006	Prospective ecological	Brazil	2200 ICU patients	Unreported culturing method. ASCs of all patients at admission to ICU and weekly thereafter. Decolonization for MRSA+ patients.	Decreased incidence of MRSA infections from 8.2% to 2.8% over 5 years, p=0.001. Decreased incidence of infection from any Staphylococcus strain from 9.9% to 3.4% over 5 years, p=0.001.	Low
Shitrit P, *et al.*[30] 2006	Interrupted time series	Israel	High-risk patients	Standard culturing method. ASCs at admission to ICU, then weekly. Contact precautions and decolonization for MRSA+ patients.	Decreased incidence of MRSA bacteremia by 50% (0.74 to 0.37 cases/1000 admissions)	Low
West TE, *et al.*[31] 2006	Interrupted time series with cost-effectiveness analysis	United States	7714 high-risk patients	Standard culturing method. ASCs at admission, then every Monday. Contact precautions if MRSA+.	No change in incidence of MRSA infections in one hospital (from 0.73 to 0.57 cases/1000 pt-days, p=0.35). Decrease in incidence of MRSA infection in a second hospital (from 0.76 to 0.45 cases/1000 pt-days, p=0.05). Combined costs of ASCs and isolation at both hospitals = $52594.62/yr. Prevented estimated 6 cases of MRSA per year that would have cost $275520/yr. Total cost savings of ASC program = $222925.38/yr.	Low

Author, Year	Study Design	Location	Sample Characteristics	Intervention	Summary of Results	Evidence Rating
Eveillard M, *et al.*[56] 2005	Before and after series	France	1% importation rate 8506 inpatients	Standard culturing method. ASCs at admission of ICU patients, then ICU+ other high-risk pts, then ICU + other high-risk pts + automatic alert system	Decreased incidence of MRSA infection by 58% over all interventions. Acquired MRSA/100 days decreased from 10% initially to 9% after ASC in ICU, to 3.8% with ASCs in ICU + high-risk patients, to 3.1% with ASCs in ICU + high-risk patients + automatic alert	Low
Lucet JC, *et al.*[37] 2005	Prospective ecological	France	8548 ICU patients	Standard culturing method. ASCs at admission, then weekly. Contact precautions for MRSA+.	Decreased incidence of MRSA infection from 7.0% to 2.8%.	Low
Nijssen S, *et al.*[38] 2005	Prospective ecological study	United States	5.7% importation rate 158 MICU patients	Standard culturing method. ASCs at admission and daily thereafter (no reporting of results or contact precautions)	No change in importation rate of colonized MRSA to the ICU. No cross contamination of MSSA or MRSA over 3 months (as detected by daily cultures). ASC + isolation would have appeared successful, but would have been falsely positive	Low

Author, Year	Study Design	Location	Sample Characteristics	Intervention	Summary of Results	Evidence Rating
Pan A, *et al.*[33] 2005	Before and After	Italy	All admitted patients	Standard culturing method. ASCs at admission, then every 3 days. Contact precautions and decolonization for all MRSA+.	Decreased incidence of MRSA bacteremia by 42% (0.64 to 0.37 cases/1000 admissions). RR 0.57 (95%CI 0.35-0.92), p = 0.03	Low
Troche G, *et al.*[39] 2005	Prospective ecological study	United States	2235 ICU patients	Standard culturing method. ASCs at admission, then weekly and at discharge. Contact precautions and decolonization if MRSA+.	Screening decreased incidence of MRSA infections. Rate decreased from 9.2 to 6.6 cases/1000 pt-days, then increased to 11.6 cases/1000 pt-days when ASC compliance dropped to 68%. With better compliance, incidence at end of study was 5.6 cases/1000 pt-days.	Low
Thompson DS, *et al.*[40] 2004	Prospective ecological	England	8.7% importation rate into ICU 1252 ICU patients	Standard culturing method. ASCs at admission to ICU, then weekly. Contact precautions and decolonization if MRSA+.	No change in incidence of MRSA infection (5.0% over course of study) No significant difference in mortality in colonized vs. infected patients (31.7% (95%CI 24.9 – 38.9) vs. 58.8% (95%CI 35.4 – 81.2).	Low
Tomic V, *et al.*[34] 2004	Before and after	Slovenia	33905 inpatients	Standard culturing method. ASCs of high-risk patients at admission, contact precautions and decolonization for MRSA+ patients, introduction of alcohol hand rub, continuous hygiene education	Decreased incidence of MRSA infections from 4.0 to 0.4 cases/1000 pt-days. Decreased proportion of acquired MRSA cases 50% to 6.1% (p<0.001 for trend)	Low

Author, Year	Study Design	Location	Sample Characteristics	Intervention	Summary of Results	Evidence Rating
Souweine B, *et al.*[35] 2000	Before and after	France	584 ICU patients	Standard culturing method. ASCs at admission, then weekly and at discharge. Contact isolation and decolonization if MRSA+. Twice weekly reminders to reinforce intervention.	Decreased incidence of MRSA infection from 5.2% to 1.7%, p=0.018 (4.0 to 2.2 cases/1000 pt-days.) No significant change in mortality attributable to MRSA infection (from 50% to 62.5%, p=0.48).	Low
Wernitz MH, *et al.*[23] 2005	Cost-benefit analysis	Germany	529 high-risk patients	Unknown culturing method. ASCs at admission, preemptive isolation and therapeutic baths until proven MRSA-	High-risk screening and isolation prevented 35 (48%) of expected cases for a net savings of 110236 euros/yr. Program cost effective if prevent 3 MRSA infections/yr. Screening universally is cost effective if 22% of screened patients are MRSA+	Moderate
Lucet JC, *et al.*[24] 2003	Cost-benefit analysis	France	4.4% importation rate into ICU 2189 ICU patients	Standard culturing method. ASCs at ICU admission	Universal screening is more beneficial than alternative high-risk screening. ASCs of all patients admitted to the ICU and preventive isolation is cost effective if importation rate is >1%.	Moderate
Gavalda L, *et al.*[26] 2006	Cost comparison	Spain	251 patients	Unknown culturing method. "proactive program to screen high-risk patients"	ASC program economically justified if it can prevent 4 MRSA infections. 49.95 euros to screen each high-risk patient vs. 2730 euros to treat MRSA infection.	Low

Author, Year	Study Design	Location	Sample Characteristics	Intervention	Summary of Results	Evidence Rating
Kim T, *et al.*[25] 2001	Cost comparison	Canada	4% importation rate 99 patients	Standard culturing method. ASCs of high-risk patients at admission.	Cost of ASC and management of colonized patients is 45% of the total costs attributed to MRSA. Cost of treating MRSA infections = 143,600 Canadian dollars/yr Costs of ASCs = 54906.50/yr and costs of managing colonized patients = 64047.50/yr. Total for preventive program 118954	Low

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